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Nitrosation of Amides Involves a Pseudopericyclic 1,3-Sigmatropic Rearrangement

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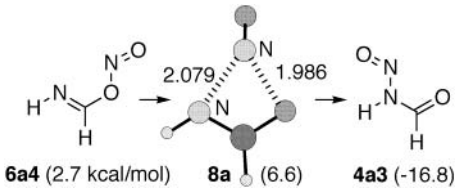
ABSTRACT



Two possible pathways for the nitrosation of formamide and *N*-methyl formamide by nitrosonium ion (NO^+) have been investigated at the B3LYP/6-31G(d,p) level. The key steps are pseudopericyclic 1,3-sigmatropic rearrangements to give the observed *N*-nitrosamides. The transition structures (8a and 8b) are close to planar on the amide moiety and have remarkably low barriers of only 6.6 and 4.8 kcal/mol from the lowest energy conformations of 6a and 6b, respectively.

The nitroso group is of great importance in a wide range of biochemical systems, ranging from signaling pathways to carcinogenesis. In particular, some *N*-nitrosamides are used as medicinal sources of NO[1] and have anticancer activity,[2] while others are potent carcinogens.[3] Nitrosonium ion (NO^+) reacts with many biological systems in a regulatory role.[4] Nitrosation of peptides generates mutagenic species.[3] An important route for the generation of *N*-nitrosamides, both in the laboratory and in vivo, is the direct reaction of nitrosonium ion (NO^+) with amides.[5] Remarkably, Rudkevich[6] and Kochi[7] have reported that NO^+ may be stabilizedby complexation with multiple aromatic rings, despite its high predilection for aromatic nitrosation.[8] Rudkevich demonstrated that encapsulation within a calix[4]arene imparts a dramatic stabilization to the reagent, to the extent of allowing it be handled in the presence of oxygen and moisture.[6] In contrast to free NO^+, the encapsulated reagent shows significant selectivity; *N*-methyl amides reacted to produce *N*-nitrosamides, but more substituted secondary amides did not.[6]

The mechanism for nitrosation of amides has been proposed to begin with attack of the nucleophilic carbonyl oxygen on NO^+.[5b,6] Rudkevich suggests that the selectivity of the encapsulated reagent toward *N*-methyl amides is a consequence of the steric constraints imposed by the necessity of the carbonyl oxygen to reach inside the cavity to react.[6] Thus, the proposed mechanism would be as summarized in eq 1. Addition of the carbonyl to NO^+ would

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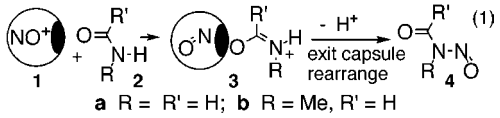
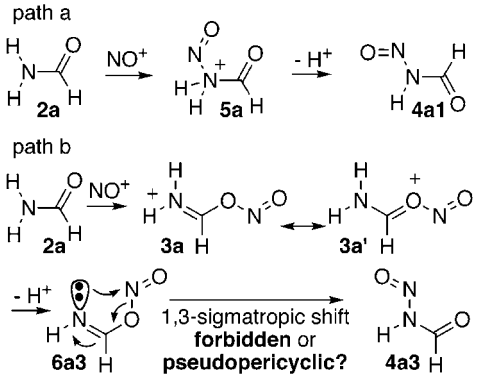
give the *O*-nitroso species **3**. Deprotonation followed by a 1,3-shift of the nitroso group would then give the observed *N*-nitrosamide, **4**.



We were intrigued by this reaction, as 1,3-shifts are relatively uncommon. Indeed, they are forbidden in hydrocarbons with a suprafacial transition state geometry[9] and are rarely observed with an antarafacial geometry. There are scattered reports from our group[10] and others[11] that there is a third possibility: a planar, pseudopericyclic transition state geometry in which there is not the cyclic orbital overlap that characterizes the classical pericyclic reaction topologies. Such reactions are always allowed and can have very low barriers. In light of this and in view of the importance of the nitrosation of amides, we undertook a computational study of this reaction at the B3LYP/6-31G(d,p) + ZPE level.[12]

We considered the two mechanistic possibilities proposed by Darbeau[5b] and by Rudkevich,[6] as shown in Scheme 1 for

Scheme 1. Possible Pathways for the Formation of *N*-Nitrosamides from Amides



R = R′ = H (designated **a** in the compound numbering). Path a involves the direct addition of the NO^+ to the amide nitrogen followed by deprotonation. While this is the simplest route to the observed product **4a1**, the intermediate **5a** is a localized cation and would be expected to be less stable than the delocalized one (**3a** and **3a′**) in path b. Although this second pathway (b) would involve the 1,3-sigmatropic rearrangement, it is indeed calculated to be the preferred pathway as described below.

The results of the calculations are summarized in Figures 1 and 2 and Table 1 for both path a and path b. All four of

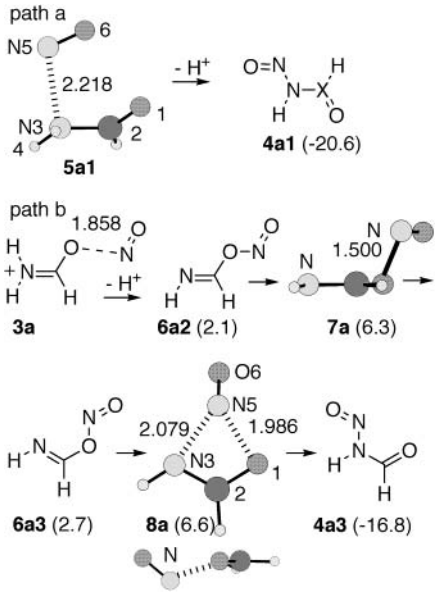


Figure 1. Pathways for the nitrosation of formamide (**2a**) as calculated at the B3LYP/6-31G(d,p) + ZPE level. Structures **5a1**, **7a**, and **8a** are shown in the calculated geometries. Carbons are shaded, oxygens are speckled, and nitrogens are labeled as such. The energies (parentheses, kcal/mol) are relative to **6a1** and include unscaled zero-point energy corrections. Distances are in Å.

the conformational possibilities around the C−N and C−O bonds were explored for **4a**. These are numbered in increasing energy from **4a1** to **4a4**. Six conformations for **6a** are similarly designated. Only the most relevant conformations are shown in Figure 1 and Table 1; the others are shown in Supporting Information. On the basis of the results for R = H, selected structures were calculated for R = Me (**b**, Figure 2).

The calculations support the expectation that direct nitrosation of the amide nitrogen would not be favorable.

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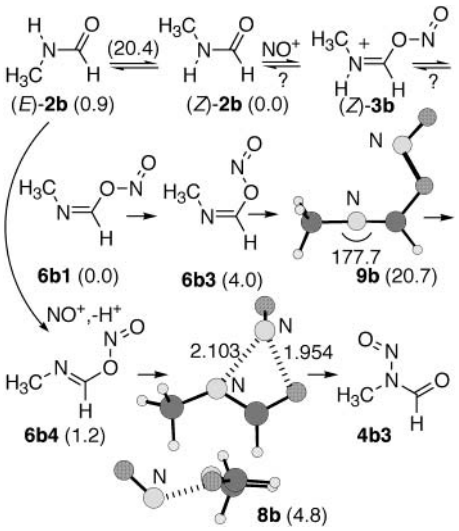

Figure 2. Pathways for the nitrosation of *N*-methyl formamide (**2b**). See Figure 1 for key. Calculated geometries of **8b** and **9b** are shown. Energies are relative to **6b1**.

Structure **5a1** is calculated to be 22.0 kcal/mol higher in energy than the *O*-nitroso cation **3a**. (An alternative conformation, **5a2**, was even higher in energy; see Supporting Information.) This clear preference for initial O-nitrosation is readily understood as reflecting the resonance stabilization of the cation **3a** relative to **5a1** as discussed above. Several aspects of the geometries are noteworthy. First, the new N−O bond in **3a** is quite long (1.858 Å) and the NO is complexed in the amide plane, allowing for resonance. In contrast, the N−O bond is even longer (2.218 Å) in **5a1** and thus makes it more like a complex than a covalent intermediate. However, no minimum was found at shorter distances. There is some pyramidalization of the amide nitrogen (the sum of the angles is 347.8°), but the near-planar geometry of the amide ($O_1-C_2-N_3-H_4$ 178.6°) suggests that significant π-delocalization remains.[13]

Table 1. Calculated Relative Energies and Lowest (or Imaginary) Frequencies of Structures Calculated at the B3LYP/6-31G(d,p) + ZPE (unscaled) Level of Theory

structure	relative energy + ZPE (kcal/mol)	lowest/imaginary[a] frequency (cm^{-1})
3a	0.0[b]	102.8
5a1	22.0[b]	115.2
4a1	−20.6[c]	135.0
4a3	−16.8[c]	177.9
6a2	2.1[c]	124.8
6a3	2.7[c]	120.2
7a	6.3[c]	162.5i
8a	6.6[c]	156.7i
(*E*)-**2b**	0.9[d]	102.8
(*Z*)-**2b**	0.0[d]	77.7
6b1	0.0[e]	79.6
6b3	4.0[e]	87.7
6b4	1.2[e]	105.3
8b	4.8[e]	94.2i
9b	20.7[e]	328.9i

[a] Transition states have one imaginary frequency. [b] Energies are relative to **3a**. [c] Energies are relative to the most stable conformation of **6a** (**6a1**, Supporting Information). [d] Energies are relative to (*Z*)-**2b**. [e] Energies are relative to the most stable conformation, **6b1**.

Deprotonation of **3a** would be expected to be facile, yielding one of several possible conformations of **6a**. The lowest energy conformation of **6a** is 2.1 kcal/mol below **6a2** (**6a1**, Supporting Information) with the amide nitrogen lone pair anti to the C−O bond. Rotation about the *O*-nitroso bond from **6a2** to **6a3** only requires an additional 4.2 kcal/mol via transition structure **7a**.

Structure **6a3** is the appropriate conformation to undergo the proposed 1,3-sigmatropic shift. As would be qualitatively predicted for a pseudopericyclic reaction, this is calculated to have a barrier only 6.6 kcal/mol above the most stable conformation of **6**. Thus, the mechanism proposed in path b is clearly quite reasonable; not only is the more stable cation **3a** formed, but the conformational interconversions and the rearrangement itself are predicted to be quite facile.

The barrier height via **8a** of only 3.9 kcal/mol above the penultimate conformation (**6a3**) is worthy of additional comment. It is quite low in absolute terms as compared to hydrocarbon closed-shell reactions. For example, the Cope is an allowed [3,3]-sigmatropic rearrangement ($\Delta H^{\ddagger} = 33.5$ kcal/mol).[14] This low barrier is even more remarkable when placed in the context of other pseudopericyclic 1,3-sigmatropic rearrangments. For example the thermoneutral 1,3-prototropic shift in a carboxylic acid has a calculated barrier of 36.6 kcal/mol, which we suggested reflects the strain of a four-membered ring.[10a] Certainly the exothermicity of the rearrangement from **6a3** to **4a1** contributes to the lower barrier of **8a**. The lengths of the breaking and forming bonds in **8a** (2.079 and 1.986 Å, respectively) are comparable to ones in other pericyclic reactions.[10,11]

As would also be expected for a pseudopericyclic reaction, the transition state **8a** is close to planar on the $O_1-C_2-N_3$ moiety (see side view in Figure 1); the $O_1-C_2-N_3-N_5$ dihedral angle is −17.9°, and the $N_3-C_2-O_1-N_5$ dihedral angle is 18.9°. The migrating nitroso group is significantly nonplanar. The $O_6-N_5-N_3$ angle is 114.0°, and the $O_6-N_5-O_1$ angle is 113.0°. These are close to the Burgi−Dunitz angle of attack on a π^* system.[15] The $N_3-N_5-O_6-O_1$ dihedral angle is 73°; this is close to the 90° that would make the forming and breaking bonds at N orthogonal. These three details suggest that the reaction involves attack of the in-plane nitrogen lone pair (N_3) of **6a3** on the N_5-O_6 π^*. Although the participation of the in-plane lone pair has been suggested by Darbeau[5b] and Rudkevich,[6] it has not been previously recognized that the reaction could have pseudopericyclic orbital disconnections on both the NO and the

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amide fragments, nor was it anticipated just how low this barrier would be.

We also studied *N*-methyl formamide (**2b**), representative of the secondary amides studied by Rudkevick.[6,16] Selected relevant structures (Figure 2 and Supporting Information) were calculated on the basis of results with **2a**. With a barrier of only 4.8 kcal/mol, the pseudopericyclic 1,3-sigmatropic rearrangement via **8b** is even more facile than without the methyl group (**8a**); the rate-determining step involves reaching the appropriate conformation **6b4**. The secondary amides are complicated by (*Z*)−(*E*) isomerization.[17] Irreversible O-nitrosation of the more stable conformation, (*Z*)-**2b**, and deprotonation of (*Z*)-**3b** would produce **6b1**, as proposed by Rudkevick.[6] While rotational interconversion with **6b3** (cf. **7a**) would be facile, the methyl group in **6b3** would interfere with the 1,3-rearrangement. A transition state for inversion at nitrogen leading to **6b4** was located (**9b**) with a barrier of 20.7 kcal/mol. This would be the rate-limiting step of the entire reaction but would still be surmountable at room temperature.

If O-nitrosation is reversible, or if the sterics of reaction with **1** require it, then reaction of the less stable conformation, (*E*)-**2b**, must also be considered. O-Nitrosation followed by deprotonation and rotation would give **6b4** directly. In this case, the lowest energy pathway is via (*E*)-**2b**, **6b4**, and the pseudopericyclic transition state **8b**, while the rate-determining step is the initial (*Z*)−(*E*) isomerization of **2b**.

In summary, the calculations are consistent with path b; initial O-nitrosation gives **3**, followed by deprotonation to give **6**. The rate-determining step involves reaching the appropriate conformation, **6a4** or **6b4**. In either case, rearrangement via **8a** or **8b** to the *N*-nitrosamides **4a** or **4b** is facile (6.6 kcal/mol or 4.8 kcal/mol, respectively). The barriers are low because the transition structures **8a** and **8b** have geometries that are favorable for attack on the nitroso group and have the energetic benefit of a pseudopericyclic geometry on both fragments.

Acknowledgment. We thank Professor Dmitry M. Rudkevich for bringing this rearrangement to our attention, the Robert A. Welch Foundation for support of this work, and the Texas Tech University High Performance Computing Center for generously providing computer time.

Supporting Information Available: Brief summary of the computational details, figures showing the geometry, and tables of the absolute energies and Cartesian coordinates of all calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) We thank a referee for suggesting this aspect of the study.

(17) Barrier for amide rotation is calculated to be 20.4 kcal/mol. The experimental gas-phase barrier is 16.5 kcal/mol (E_{act}); barriers in solution are slightly higher. Ross, B. D.; True, N. S.; Matson, G. B. *J. Phys. Chem.* **1984**, *88*, 2675−2678.